

MR Spectroscopy in Clinical Practice

Therapy planning and follow-up of adult brain tumors

Alberto Bizzi, M.D.

Istituto Nazionale Neurologico "Carlo Besta" - Milan, Italy

Conventional MR imaging shows abnormalities in all patients with brain tumor and it is diagnostic of tumor in the majority of cases. The high sensitivity of MRI, its high spatial resolution and multiplanar capability lead to superb tumor localization. In many cases MRI is able to give a correct diagnosis of tumor type. This is mainly based on age of the patient, tumor location and extension, T1 and T2 relaxation properties and response to contrast agent administration. The presence of cysts, necrosis, calcifications or hemorrhagic components and the age of the patient are additional important informations. Open surgery is the treatment of choice in most patients with a cerebral mass lesion, and a histopathological diagnosis will eventually be obtained.

Given the above considerations, what is the role of clinical H-Magnetic Resonance Spectroscopy in the evaluation of brain tumors?

The specificity of MRI still lags behind its sensitivity and anatomic depiction. MRI provides significant more information about intrinsic tissue characterization than tumor biology. H-MRS adds relevant metabolic informations about signal changes of several metabolites: choline (3.21 ppm), creatine (3.04 ppm), NAA (2.02 ppm), lactate (1.34 ppm), myo-inositol (3.54 ppm), alanine (1.48 ppm) and mobile lipids (1.4 and 0.9 ppm). Brain tumors are heterogeneous lesions and the multivoxel H-MRSI technique is the method of choice to study metabolic regional differences (1, 2).

The aim of this presentation is to critically review the contribution of H-MRS in determining tumor type and degree of malignancy. The role of multivoxel H-MR Spectroscopic Imaging in assisting neurosurgeons and radiotherapists to plan therapy and follow-up response to therapy will also be addressed.

Non-neoplastic lesions

In clinical practice it is considered an exception when conventional MRI cannot differentiate a tumor from a non-neoplastic lesion. An isolated giant demyelinating plaque, an inflammatory non demyelinating lesion, an unusual case of focal cortical dysplasia or of ischemic infarct, may occasionally enter the differential diagnosis with a brain tumor. In unusual cases it is appropriate to request an

H-MRS study. The proton MR spectrum of brain tumors clearly differs from that of normal brain: the elevation of the choline signal is the most consistent feature of a tumor, and it is associated with moderate or severe NAA signal loss and variable changes in creatine, lactate and lipids. Elevated choline has been detected in all brain tumors, with few anecdotic exceptions (3). The H-MR spectrum of infarct shows moderate NAA signal loss, with unchanged choline and creatine signal; an elevated lactate signal may be found in acute and subacute lesions (4). The spectrum of focal cortical dysplasia may mimic normal brain. The differentiation of a spectrum of an isolated demyelinating plaque from that of a brain tumor is more controversial (5). In the acute stage a demyelinating plaque may show variable elevation in choline and myo-inositol, mild NAA signal loss and accumulation of lactate. NAA signal loss correlates with reduction in axonal density; concomitant increases of choline and myo-inositol correspond to predominant fibrillary gliosis (6). During the course of the disease, choline and NAA abnormalities may reverse (7). With protoplasmic gliosis becoming more prominent in remyelinating and active demyelinating lesions, choline and myo-inositol are less elevated (6). As a practical rule, the finding of a very high choline signal without elevated myo-inositol is more frequently found in tumors than in a demyelinating lesions.

Cerebral abscess

H-MRS is often requested to clarify the nature of a ring-enhancing mass lesion. The MRI features of a brain abscess are similar to those of a necrotic tumor: glioblastoma multiforme or metastasis. Single voxel H-MRS at short TE has been shown to be quite sensitive in identifying intermediate bacterial metabolites in the core of the lesion (8, 9, 10). Pyogenic bacteria produce large amounts of hydrolytic enzymes, resulting in high concentrations of proteins and amino acids: glycine (3.56 ppm), succinate (2.42 ppm), acetate (1.92 ppm), alanine (1.48 ppm), lactate (1.34 ppm), and other amino acids (leucine, isoleucine, and valine at 0.9 ppm) have been reported in pyogenic abscesses. The finding of lactate and lipids without amino acids is less specific and it is found in tuberculous abscesses (10) and necrotic tumors (8). The use of the multivoxel H-MRSI technique will increase specificity by examining the adjacent tissue for elevation of choline, which is not a feature of cerebral abscess and it may indicate presence of neoplastic cells in a necrotic tumor.

Differential diagnosis between GBM and metastasis

The capability of H-MRS to differentiate glioblastoma multiforme (GBM) from metastasis or lymphoma is also controversial. Most authors believe that there is so much overlapping between the MRS

profiles of these tumor types, that it is not possible to distinguish among them with certainty. Both tumors show high levels of choline, associated with marked creatine and NAA signal loss. The detection of elevated mobile lipids is common in metastasis (and lymphoma), and it is occasionally present in the necrotic center of a GBM. Multivoxel H-MRSI has the advantage of evaluating not only the core of the lesion but also the surrounding tissue with T2W signal abnormality. The presence of voxels with elevated choline outside of the enhancing ring is in favour of GBM rather than metastasis.

Meningiomas

Meningiomas are extraaxial tumors and they are easily diagnosed by MRI. The choline signal is usually quite elevated in meningioma and it is associated with complete absence of creatine and NAA. The finding of an additional peak at 1.48 ppm (alanine) may confirm the diagnosis.

Grading of gliomas

Diffusely infiltrating gliomas are the most frequent intracranial neoplasms. Astrocytomas account for more than 60% of all primary brain tumors; oligodendrogliomas for about 5-18%, ependymoma for 6-12%. The prognosis and the length of a recurrence-free survival after surgery are closely related to the intrinsic biology of the neoplasm. The goal of surgery in patients with a new diagnosed brain tumor is to remove most of the mass and to obtain a histopathological diagnosis. Important decisions on additional treatment will depend on the tumor type and grade of malignancy. The ideal neuroimaging technique will have to provide to the oncologist the following biological information: rate of growth, heterogeneity and extension of the tumor, and sensitivity to current treatment strategies (i.e., radiotherapy, chemotherapy, angiogenesis inhibitors, etc.). The choline signal is an index of phospholipid turnover and cellular density and it is significantly increased in all gliomas. Grading of gliomas by H-MRS remains controversial (2, 13-16). It has been shown that using pattern analysis of H-MRSI data improves accuracy of pre-operative diagnosis of brain tumors (17-18). Multiple groups have shown that the choline signal in the solid component of gliomas is higher in grade III and IV than in grade II astrocytoma; choline is relatively diminished in areas of prevalent necrosis, and wide overlapping among grades prevents accurate grading of gliomas in the individual case (1-2, 15). As a practical rule, diffuse (WHO grade II) astrocytomas have mild choline elevation, anaplastic (WHO III) astrocytomas have very high choline levels that sometimes can be higher than GBM. One exception to this rule may be represented by oligodendrogliomas that show a larger spectrum with marked

choline elevation in few cases. On the contrary when a very high choline signal is associated with severe NAA and creatine signal losses the diagnosis of a low grade astrocytoma is unlikely. Another exception may be represented by moderate elevation of creatine in association with choline (19). The presence of lactate is more common in high grade glioma, nevertheless it can be found in low grade glioma and it is not a discriminator of grade (2, 15). Mobile lipid resonances at 1.3 and 0.9 ppm are found in GBM and metastases and their signal increases with the extent of extracellular necrosis (20).

Therapy planning

Positron Emission Tomography (PET) has been the method of choice for preoperative evaluation of glioma metabolism. SPECT with thallium-201 has also been used to measure cell growth rate of gliomas. Both these methods use radioactive isotopes, are less accessible than MR techniques and the coregistration of these images with MRI takes time. Multivoxel H-MRSI is less expensive and far more accessible than the above techniques. The metabolic information on rate of growth, tumor heterogeneity and extension provided by H-MRSI is unique and relevant and it can be acquired during the same study session.

H-MRSI data from many groups are consistent in showing that areas with higher choline levels have higher proliferation index (21-22) and higher cellular density (23-25). Multivoxel H-MRSI identifies the intratumoral region with the highest choline signal and in heterogeneous lesions it may help define the optimal site from which to obtain tissue sampling at surgery or with a needle stereotactic biopsy (25). Co-registration of H-MRSI data sets with conventional MRI and export into a frameless neuronavigational device has been achieved (26). H-MRSI easily confirms areas of macroscopic necrosis within the tumor that is a poor prognostic sign. H-MRSI appears more accurate than conventional MRI in defining tumor boundary and quantifying the degree of tumor infiltration (27). The finding of normal MR spectra in areas with abnormal signal intensity on T2-weighted MR images in the proximity of the tumor suggests peritumoral edema. The finding of elevated choline in areas away from the bulk of the tumor suggests tumor extension and multicentricity of the lesion. One study (28) has shown that, despite the area with T2-weighted signal abnormality at risk for microscopic disease can be as much as 50% greater than the area estimated by H-MRSI, metabolically active tumor still extended outside the T2 abnormal region in the majority of cases. The use of H-MRSI to define target volumes for radiotherapy planning may change the location of the volume receiving a boost dose as well as reduce the volume receiving a standard dose (28). H-MRSI may monitor tumor response during

treatment (29-30). Current limitations in spatial resolution will be overcome with shorter acquisition times secondary to improvements in software and coil design and with improving signal-to-noise and spectral resolution at higher field strength. At the end of a H-MRS tumor study, a perfusion MR study can be added; the perfusion MR images can be easily coregistered with the metabolic information obtained by H-MRSI. Perfusion MR measures tumor regional cerebral blood volume (rCBV) and permeability, which are related to angiogenesis.

Recurrent tumor and delayed radiation necrosis

The appearance of a new enhancing lesion or growth of a residual one in a patient, who had surgery and radiotherapy, suggest recurrent tumor or delayed radiation necrosis (DRN). Onset of DRN is usually from 6 months to 2 years after treatment, and its occurrence is dependent on both dosage and rate of delivery. It is self-limited and does not require surgical decompression or further treatment unless significant mass effect develops. Both DRN and recurrent tumor are frequently found in the proximity of the original tumor bed and they have similar characteristics on MRI. To make things more difficult, they can frequently coexist. On pathologic examination they can easily be distinguished, but biopsy sampling is limited. The H-MRSI spectrum of DRN shows severe signal loss of all main metabolites with the variable appearance of strong mobile lipid signals at 1.3 and 0.9 ppm (31-32). This finding alone indicates the presence of necrosis within the lesion and it is not sufficient to rule out recurrent tumor. In ambiguous cases by MRI, the challenge for H-MRSI is to rule out the presence of elevated choline in voxels inside and around the lesion. FDG-PET and perfusion MR imaging may add complementary physiologic information to MRI and H-MRSI. In difficult cases, the combined use of multiple neuroimaging techniques may increase the diagnostic accuracy.

In conclusion,

H-MRSI's role in the clinical evaluation of brain tumors has been receiving increased attention from neurosurgeons, radiation and medical oncologists. The number of neuroradiologists that have integrated the technique into the routine evaluation of brain tumors is increasing. For practical purposes I've attached a table with the expected average signal changes for the non-neoplastic and neoplastic lesions discussed in this presentation. The following practical statements may prove useful in clinical practice: 1) a lesion to be a tumor must have elevated choline signal; 2) the choline signal is higher in the faster growing (solid) component of the tumor; 3) the presence of mobile lipids indicate extracellular necrosis; 4) lactate is more often found in anaplastic gliomas but it is a "non-specific" finding.

Alberto Bizzi, M.D.
 Dept. of Neuroradiology
 Istituto Nazionale Neurologico "Carlo Besta"
 Via Celoria, 11
 20133 Milano, Italy
 email: alberto_bizzi@fastwebnet.it

Table

Non-neoplastic		Cho	Cr	NAA	Lac	Lip	Others	
MS plaque		+	=	- -	+	ND	ND	
Subacute infarct		=	=	-	+	ND	ND	
Focal cortical dysplasia		=	=	=	ND	ND	ND	
Pyogenic abscess		- -	- - -	- - -	+	+	Acetate	
Delayed Radiation Necrosis		-	- - -	- - -	ND	+	ND	
Peritumoral edema		=	-	-	ND	ND	ND	
Neoplastic		WHO	Cho	Cr	NAA	Lac	Lip	Others
Pilocytic Astrocytoma		I	+	- -	-- -	ND	ND	ND
Diffuse Astrocytoma		II	+	=	- -	ND	ND	ND
Oligodendroglioma		II/III I	+++	- - -	- -	ND	ND	ND
Anaplastic Astrocytoma		III	+++	-	- -	+	ND	ND
GBM		IV	+++	- - -	- - -	+	+	ND
Ependymoma			+++	- - -	- - -	ND	ND	ND
Medulloblastoma			+++	- - -	- - -	ND	ND	ND
Meningioma			+++	- - -	- - -	ND	ND	Alanine
Metastasis			++	- - -	- - -	ND	++	ND
Lymphoma			+++	- - -	- - -	ND	++	ND

Legend:

The expected average signal change for each category are indicated:

mild signal elevation (+); moderate (++); severe (+++);
 mild signal loss (-); moderate (--), severe (---);
 normal, unchanged signal (=); not detectable (ND).

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